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(54) Method for preventing a second heart attack employing and HMG CoA reductase inhibitor.

(57) A method is provided for preventing or reducing the risk of a second heart attack by administering an HMG CoA reductase inhibitor such as pravastatin, alone or in combination with an ACE inhibitor.

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The present invention relates to a method for preventing or reducing the risk of a second heart attack by administering an HMG CoA reductase inhibitor, such as pravastatin, alone or in combination with an ACE inhibitor.

It is well established that lipid disorders are important factors in the development of coronary heart disease (CHD), Schettler, G., "The role of diet and drugs in lowering serum cholesterol in the postmyocardial infarction patient," Cardiovasc. Drugs Ther., 1989, 2/6 (795-799).

Glatter, T.R., "Hyperlipidemia. What is 'normal', who should be treated and how," Postgrad. Med., 1984, 76/6 (49-59), states that "As the Coronary Primary Prevention Trial has recently shown, a 1% reduction in cholesterol level produces a 2% reduction in risk of myocardial infarction."

Goldstein, J.L., et al, "The LDL receptor defect in familial hypercholesterolemia. Implications for pathogenesis and therapy," Med. Clin. North Am., 1982, 66/2 (335-362) indicate that "familial hypercholesterolemia was the first genetic disorder recognized to cause myocardial infarction. To this day, it remains the outstanding example of a single gene mutation that causes both hypercholesterolemia and coronary atherosclerosis."

Satler, L.F., et al, "Reduction in coronary heart disease: Clinical and anatomical considerations," Clin. Cardiol., 1989, 12/8 (422-426) disclose that "the higher the total plasma cholesterol and low density lipoprotein cholesterol (LDL-C), the greater the risk that coronary artery disease will develop. Recently, clinical trials including the Coronary Drug Project, the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), and the Helsinki Heart Study provided evidence that lowering cholesterol reduces the frequency of fatal and nonfatal coronary events." In addition, Satler et al disclose that other studies "demonstrated that lowering of cholesterol was associated with a decreased incidence of progression of coronary disease, as well as with the potential for reduction in the atherosclerotic plaque."

Wilhelmsen, L., "Practical guidelines for drug therapy after myocardial infarction," Drugs, 1989, 38/6 (1000-1007) discloses that it is advisable to correct blood lipid disturbances in effective management of the postinfarction patient.

Yamamoto, A. et al, "Clinical features of familial hypercholesterolemia," Arteriosclerosis, Jan.-Feb. 1989, 9 (1 Suppl.) p I66-74, disclose that "in addition to the low density lipoprotein (LDL) cholesterol level, higher triglyceride and lower high density lipoprotein (HDL) cholesterol levels correlate with an increased risk of ischemic heart diseases."

There are several different classes of compounds which have serum cholesterol lowering properties. Some of these compounds are inhibitors of the enzyme HMG CoA reductase which is essential in the production of cholesterol, such as mevastatin (disclosed in U. S. Patent No. 3,983,140), lovastatin also referred to as mevinolin (disclosed in U.S. Patent No. 4,231,938), pravastatin (disclosed in U.S. Patent No. 4,346,227) and velostatin also referred to as synvinolin (disclosed in U. S. Patents Nos. 4,448,784 and 4,450,171).

Other compounds which lower serum cholesterol may do so by an entirely different mechanism than the HMG CoA reductase inhibitors. For example, serum cholesterol may be lowered through the use of bile acid sequestrants such as cholestyramine, colestipol, DEAE-Sephadex and poly(diallylmethylamine) derivatives (such as disclosed in U. S. Patents Nos. 4,759,923 and 4,027,009) or through the use of antihyperlipoproteinemics such as probucol and gemfibrozil which apparently lower serum "low density lipoproteins" (LDL) and/or converts LDL into high density lipoproteins (HDL).

Angiotension-converting enzyme inhibitors (ACE inhibitors) such as captopril and enalapril and known antihypertensive agents and, in addition, are known for their cardioprotective effects and for treating congestive heart failure.

European Patent Application 0219782 to Scholkens (Hoechst) discloses the treatment of atherosclerosis, thrombosis and/or peripheral vascular disease in mammals using an angiotensin converting enzyme (ACE) inhibitor or its physiologically tolerable salts. It further discloses that because ACE is predominantly localized in the luminal plasma membrane of the endothelial cell, ACE inhibitors can interfere in platelet-endothelium interaction. In addition, Scholkens dislcoses that ACE inhibition potentiates the action of bradykinin (a strong stimulator of prostacyclin release from endothelial cells) by inhibiting its degradation and ACE inhibitors, consequently, have an inhibitory effect on platelet aggregation.

Cecil, Textbook of Medicine, 16 Ed., pp 239 to 241, indicates at page 240 that blood pressure is an accelerator of atherosclerosis.

U.S. Patent Nos. 4,046,889 and 4,105,776 to Ondetti et al disclose proline derivatives, including captopril, which are angiotensin converting enzyme (ACE) inhibitors useful for treating hypertension.

U.S. Patent No. 4,337,201 to Petrillo discloses phosphinylalkanoyl substituted prolines, including fosinopril, which are ACE inhibitors useful for treating hypertension.

U.S. Patent No. 4,374,829 discloses carboxyalkyl dipeptide derivatives, including enalapril, which are

ACE inhibitors useful for treating hypertension.

U.S. Patent No. 4,452,790 to Karanewsky et al discloses phosphonate substituted amino or imino acids and salts thereof and covers (S)-1-[6-amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]-oxy]-1-oxohexyl]-L-proline (SQ 29,852, ceranapril). These compounds are ACE inhibitors useful in treating hypertension.

U.S. Patent No. 4,316,906 to Ondetti et al discloses ether and thioether mercaptoacyl prolines which are ACE inhibitors useful in treating hypertension. This Ondetti et al patent covers zofenopril.

In accordance with the present invention, a method is provided for preventing onset of or reducing risk of a second heart attack in a mammalian species, wherein a therapeutically effective amount of an HMG CoA reductase inhibitor, alone or in combination with an ACE inhibitor, is administered systemically, such as orally or parenterally.

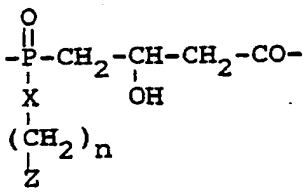
In preferred embodiments where the patient to be treated in accordance with the present invention is normotensive, the angiotensin converting enzyme inhibitor, where employed, will preferably be administered in amounts below that required to cause hemodynamic effects, that is below that required to cause a reduction in blood pressure.

The combination of the HMG CoA reductase inhibitor and ACE inhibitor will be employed in a weight ratio to each other of within the range of from about 0.001:1 to about 1000:1 and preferably from about 0.05:1 to about 100:1.

The HMG CoA reductase inhibitor, alone or in combination with the ACE inhibitor will be administered as soon as possible after the initial myocardial infarction.

The HMG CoA reductase inhibitors suitable for use herein include, but are not limited to, mevastatin and related compounds as disclosed in U. S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds as disclosed in U. S. Patent No. 4,231,938, pravastatin and related compounds such as disclosed in U. S. Patent No. 4,346,227, velostatin (synvinolin) and related compounds as disclosed in U. S. Patents Nos. 4,448,784 and 4,450,171, with lovastatin, pravastatin or velostatin being preferred. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluindostatin (Sandoz XU-62-320), pyrazole analogs of mevalonolactone derivatives as disclosed in U. S. Patent No. 4,613,610, indene analogs of mevalonolactone derivatives as disclosed in PCT application WO 86/03488, 6-[2-(substituted-pyrrol-1-yl)alkyl]-pyran-2-ones and derivatives thereof as disclosed in U. S. Patent No. 4,647,576, Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives as disclosed in French Patent No. 2,596,393, 2,3-di-substituted pyrrole, furan and thiophene derivatives as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone as disclosed in U. S. Patent No. 4,686,237, octahydro-naphthalenes such as disclosed in U. S. Patent No. 4,499,289, keto analogs of mevinolin (lovastatin) as disclosed in European Patent Application No. 0,142,146 A2, as well as other known HMG CoA reductase inhibitors.

In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase suitable for use herein are disclosed in GB 2205837 which compounds have the moiety



wherein X is -O- or -NH-, n is 1 or 2 and Z is a hydrophobic anchor.

Examples of such compounds include (S)-4-[[[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]methoxy]-methoxyphosphinyl]-3-hydroxy-butanoic acid, methyl ester or its monolithium salt,

(S)-4-[[[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]methoxy]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt,

(3S)-4-[[[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]methoxy]methylphosphinyl]-3-hydroxybutanoic acid, monolithium salt,

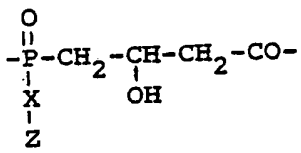
(S)-4-[[[2,4-dichloro-6-[(4-fluorophenyl)-methoxy]phenyl]methoxy]methoxyphosphinyl]-3-hydroxybutanoic acid, monolithium salt,

(3S)-4-[[[2,4-dichloro-6-[(4-fluorophenyl)-methoxy]phenyl]methoxy]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt,

(3S)-4-[[2,4-dichloro-6-[(4-fluorophenyl)-methoxy]phenyl]methoxy]methylphosphinyl]-3-hydroxybutanoic acid, or its methyl ester, and

(S)-4-[[[[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl-2-yl]methyl] amino]methoxyphosphinyl]-3-hydroxybutanoic aicd, monolithium salt.

Another class of HMG CoA reductase inhibitors suitable for use herein include phosphinic acid compounds disclosed in GB 2205838, which compounds have the moiety



wherein X is $-CH_2-$ $-CH_2-CH_2-$, $-CH=CH-$, $-CH_2CH_2CH_2-$, $-C\equiv C-$ or $-CH_2O-$, where O is linked to Z, and Z is a hydrophobic anchor.

Examples of such compounds include (S)-4-[[[1-(4-fluorophenyl)-3-(1-methylethyl)-1H-indol-2-yl]-ethynyl]hydroxyphosphinyl]-3-hydroxyfutanoic acid, or its sodium salt (SQ 33,600) (preferred) or its dilithium salt;

(S)-4-[[(E)-2-[4'-fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt;

(S)-4-[[2-[4'-fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, methyl ester or mono- or di-alkali metal salts thereof;

(S)-4-[[[4'-fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl]ethynyl]methoxyphosphinyl]-3-hydroxybutanoic acid or the methyl ester thereof;

(5Z)-4-[[2-[4'-fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, methyl esters thereof;

(S)-4-[[2-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]ethyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl esters;

(S)-4-[[2-[[1,1'-biphenyl]-2-yl]ethyl]methoxyphosphinyl-3-hydroxybutanoic acid, methyl ester;

(S)-4-[[2-[4'-fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;

(S)-4-[[2-[4'-fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;

(SZ)-4-[[2-[4'-fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;

(S)-4-[[2-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;

(S)-4-[[2-[(1,1'-biphenyl]-2-yl]ethyl]hydroxyphosphinyl]-3-butanoic acid, dilithium salt;

(S)-4-(hydroxymethoxyphosphinyl)-3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]butanoic acid, methyl ester, or its dicyclohexylamine (1:1) salt;

(S)-4-[[2-[1-(4-fluorophenyl)-3-(1-methylethyl)-1-indol-2-yl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or disodium salt or methyl ester thereof;

(E)-4-[[2-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

4-[[2-[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

(E)-4-[[2-[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

(S)-4-[[[2,4-dimethyl-6-[(4-fluorophenyl)-methoxy]phenyl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

(S)-4-[[[2,4-dimethyl-6-[(4-fluorophenyl)-methoxy]phenyl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

(S)-4-[[2-[3,5-dimethyl[1,1'-biphenyl)-2-yl]ethyl)hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

(S)-4-[[2-[4'-fluoro-3,5-dimethyl[1,1'-biphenyl]-2-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;

(S)-4-[[2-[[1,1'-biphenyl]-2-yl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or

methyl ester thereof;
(S)-4-[[2-(5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethynyl]methoxy phosphinyl]-3-hydroxybutanoic acid, methyl ester;
(S)-4-[[2-[1-(4-fluorophenyl)-3-(1-methylethyl)-1H-indol-2-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
(S)-4-[[2-[5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;
(E)-4-[[2-[5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethenyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;
(E)-4-[[2-[5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;
(S)-4-[[2-[5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;
(S)-4-[[2-[5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;
(S)-4-[[2-[3-(4-fluorophenyl)-5-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;
(S)-4-[[2-[3-(4-fluorophenyl)-5-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;
(S)-4-[[2-[3-(4-fluorophenyl)-5-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethynyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;
(S)-4-[[2-[3-(4-fluorophenyl)-5-(1-methylethyl)-1-phenyl-1H-pyrazol-4-yl]ethynyl]hydroxy phosphinyl]-3-hydroxybutanoic acid, dilithium salt;
(S)-4-[[[4-(4-fluorophenyl)-1-(1-methylethyl)-3-phenyl-1H-pyrazol-5-yl]ethynyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;
(S)-4-[[[4-(4-fluorophenyl)-1-(1-methylethyl)-3-phenyl-1H-pyrazol-5-yl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;
(S)-4-[[2-[4-(4-fluorophenyl)-1-(1-methylethyl)-3-phenyl-1H-pyrazol-5-yl]ethyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;
(S)-4-[[2-[4-(4-fluorophenyl)-1-(1-methylethyl)-3-phenyl-1H-pyrazol-5-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;
(S)-4-[[[1-(4-fluorophenyl)-4-(1-methylethyl)-2-phenyl-1H-imidazole-5-yl]ethynyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;
(S)-4-[[[1-(4-fluorophenyl)-4-(1-methylethyl)-2-phenyl-1H-imidazol-5-yl]ethynyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;
(S)-4-[[2-[1-(4-fluorophenyl)-4-(1-methylethyl)-2-phenyl-1H-imidazol-5-yl]ethyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;
(S)-4-[[2-[1-(4-fluorophenyl)-4-(1-methylethyl)-2-phenyl-1H-imidazol-5-yl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;
(S)-4-[[[2-(cyclohexylmethyl)-4,6-dimethylphenyl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
4-[[2-[2-(cyclohexylmethyl)-4,6-dimethylphenyl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
(S)-4-[[2-[2-(cyclohexylmethyl)-4,6-dimethylphenyl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
4-[[[[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]oxy]methyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
4-[[[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]methyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
(S)-4-[[[1-(4-fluorophenyl)-3-methyl-2-naphthalenyl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
(E)-4-[[2- [1-(4-fluorophenyl)-3-methyl-2-naphthalenyl]ethenyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
(S)-4-[[2-[1-(4-fluorophenyl)-3-methyl-2-naphthalenyl]ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid or its dilithium salt or methyl ester thereof;
4-[[3-[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]propyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;
4-[[3-[4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl]propyl]hydroxyphosphinyl]-3-hydroxybutanoic acid,

dilithium salt;

[1S-[1α(R*),2α,4aβ,8β,8aα]]-4-[[2-[8-(2,2-dimethyl-1-oxobutoxy)decahydro-2-methyl-1-naphthalenyl]-ethyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester;

[1S-[1α(R*),2α,4aβ,8β,8aβ]]-4-[[2-[8-(2, 2-dimethyl-1-oxobutoxy)decahydro-2-methyl-1-naphthalenyl]-ethyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt;

(S)-4-[[[3'-(4-fluorophenyl)spiro]cyclopentane-1,1'-[1H]indene]-2-yl]ethynyl]methoxyphosphinyl]-3-hydroxybutanoic acid, methyl ester; and

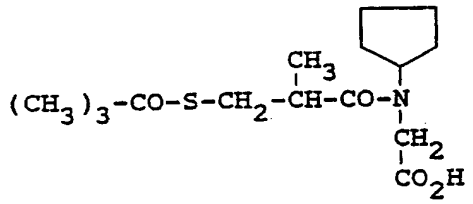
(S)-4-[[[3'-(4-fluorophenyl)spiro]cyclopentane-1,1'-[1H]indene]-2-yl]ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, dilithium salt.

Preferred are pravastatin or SQ 33,600.

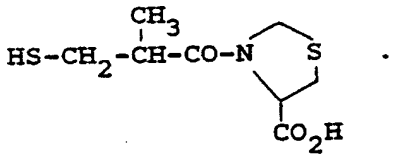
The above-mentioned U.S. patents are incorporated herein by reference.

The angiotensin converting enzyme inhibitor which may be employed herein preferably includes those containing a mercapto (-S-) moiety such as substituted proline derivatives, such as any of those disclosed in U. S. Patent No. 4,046,889 to Ondetti et al mentioned above, with captopril, that is, 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline, being preferred, and mercaptoacyl derivatives of substituted prolines such as any of those disclosed in U. S. Patent No. 4,316,906 with zofenopril being preferred.

Other examples of mercapto containing ACE inhibitors that may be employed herein include rentiapril (fentiapril, Santen) disclosed in Clin. Exp. Pharmacol. Physiol. 10:131 (1983); as well as pivopril, that is



and Y5980, that is



Other examples of angiotensin converting enzyme inhibitors which may be employed herein include any of those disclosed in U.S. patent No. 4,374,829 mentioned above, with N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline, that is, enalapril, being preferred, any of the phosphonate substituted amino or imino acids or salts disclosed in in. S. Patent No. 4,452,790 with (S)-1-[6-amino-2-[[hydroxy-(4-phenylbutyl)-phosphinyl]oxy]-1-oxohexyl]-L-proline (SQ 29,852 or ceranapril) being preferred, phosphinylalkanoyl prolines disclosed in U. S. Patent No. 4,168,267 mentioned above with fosinopril being preferred, any of the phosphinylalkanoyl substituted prolines disclosed in U . S. Patent No. 4,337,201, and the phosphonamidates disclosed in U . S. Patent No. 4,432,971 discussed above.

Other examples of ACE inhibitors that may be employed herein include Beecham's BRL 36,378 as disclosed in European patent Nos. 80822 and 60668; Chugai's MC-838 disclosed in CA. 102:72588v and Jap. J. Pharmacol. 40:373 (1986); Ciba-Geigy's CGS 14824 (3-([1-ethoxycarbonyl-3-phenyl-(1S)-propyl]-amino)-2,3,4,5-tetrahydro-2-oxo-1-(3S)-benzazepine-1 acetic acid HCl) disclosed in U.K. Patent No. 2103614 and CGS 16,617 (3(S)-[[(1S)-5-amino-1-carboxypentyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-ethanoic acid) disclosed in U. S. Patent No. 4,473,575; cetapril (alacepril, Dainippon) disclosed in Eur. Therap. Res. 39:671 (1986); 40:543 (1986); ramipril (Hoechst) disclosed in Eur. Patent No. 79-022 and Curr. Ther. Res. 40:74 (1986); Ru 44570 (Hoechst) disclosed in Arzneimittelforschung 35:1254 (1985), cilazapril (Hoffman-LaRoche) disclosed in J. Cardiovasc. Pharmacol. 9:39 (1987); R_o 31-2201 (Hoffman-LaRoche) disclosed in FEBS Lett. 165:201 (1984); lisinopril (Merck) disclosed in Curr. Therap. Res. 37:342 (1985) and Eur. patent appl. No. 12-401, indalapril (delapril) disclosed in U. S. Patent No. 4,385,051; indolapril

(Schering) disclosed in J. Cardiovasc. Pharmacol. 5:643, 655 (1983); spirapril (Schering) disclosed in Acta. Pharmacol. Toxicol. 59 (Supp. 5):173 (1986); perindopril (Servier) disclosed in Eur. J. Clin. Pharmacol. 31:519 (1987); guinapril (Warner-Lambert) disclosed in U. S. Patent No. 4,344,949 and CI 925 (Warner-Lambert) ([3S-[2[R(*)R(*)]]3R(*)]-2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino[-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid HCl) disclosed in Pharmacologist 26:243, 266 (1984), WY-44221 (Wyeth) disclosed in J. Med. Chem. 26:394 (1983).

Preferred are those ACE inhibitors which are proline or substituted proline derivatives and most preferred are such ACE inhibitors which include a mercapto group.

The above-mentioned U.S. patents are incorporated herein by reference.

In carrying out the method of the present invention, the HMG CoA reductase inhibitor alone or in combination with the ACE inhibitor may be administered to mammalian species, such as dogs, cats, humans, etc., and as such may be incorporated in a conventional systemic dosage form, such as a tablet, capsule, elixir or injectable. The above dosage forms will also include the necessary carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol), anti-oxidants (ascorbic acid of sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral forms are quite satisfactory as well.

The dose administered must be carefully adjusted according to age, weight and condition of the patient, as well as the route of administration, dosage form and regimen and the desired result.

Thus, for oral administration, a satisfactory result may be obtained employing the HMG CoA reductase inhibitor in dosages employed, for example, for lovastatin as indicated in the Physician's Desk Reference, such as in an amount within the range of from about 1 to 2000 mg, and preferably from about 4 to about 200 mg.

A preferred oral dosage form, such as tablets or capsules, will contain the HMG CoA reductase inhibitor in an amount of from about 0.5 to about 100 mg, preferably from about 5 to about 80 mg, and more preferably from about 10 to about 40 mg.

With regard to the ACE inhibitor, for oral administration, a satisfactory result may be obtained employing the ACE inhibitor in an amount within the range of from about 0.01 mg/kg to about 100 mg/kg and preferably from about 0.1 mg/kg to about 5 mg/kg.

A preferred oral dosage form , such as tablets or capsules, will contain the ACE inhibitor in an amount of from about 0.1 to about 500 mg, preferably from about 2 to about 50 mg, and more preferably from about 10 to about 25 mg.

For parenteral administration, the ACE inhibitor will be employed in an amount within the range of from about 0.005 mg/kg to about 10 mg/kg and preferably from about 0.005 mg/kg to about 2 mg/kg.

The HMG CoA reductase inhibitor and ACE inhibitor may be employed together in the same oral dosage form or in separate oral dosage forms taken at the same time.

The compositions described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily. It may be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

Tablets of various sizes can be prepared, e.g., of about 2 to 2000 mg in total weight, containing one or both of the active substances in the ranges described above, with the remainder being a physiologically acceptable carrier of other materials according to accepted pharmaceutical practice. These tablets can, of course, be scored to provide for fractional doses. Gelatin capsules can be similarly formulated.

Liquid formulations can also be prepared by dissolving or suspending one or the combination of active substances in a conventional liquid vehicle acceptable for pharmaceutical administration so as to provide the desired dosage in one to four teaspoonsful.

The compositions described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily. It may be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

Liquid formulations can also be prepared by dissolving or suspending one or the combination of the active substances in a conventional liquid vehicle acceptable for pharmaceutical administration so as to provide the desired dosage in one to four teaspoonsful.

Such dosage forms can be administered to the patient on a regimen of one to four doses per day.

According to another modification, in order to more finely regulate the dosage schedule, the active substances may be administered separately in individual dosage units at the same time or carefully coordinated times. Since blood levels are built up and maintained by a regulated schedule of administration, the same result is achieved by the simultaneous presence of the two substances. The respective substances can be individually formulated in separate unit dosage forms in a manner similar to that described above.

Fixed combinations of HMG CoA reductase inhibitor and ACE inhibitor are more convenient and are preferred, especially in tablet or capsule form for oral administration.

In formulating the compositions, the active substances, in the amounts described above, are compounded according to accepted pharmaceutical practice with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in the particular type of unit dosage form.

Illustrative of the adjuvants which may be incorporated in tablets are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate or cellulose; a disintegrating agent such as corn starch, potato starch, alginic acid or the like; a lubricant such as stearic acid or magnesium stearate; a sweetening agent such as sucrose, aspartame, lactose or saccharin; a flavoring agent such as orange, peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets or capsules may be coated with shellac, sugar or both. A syrup of elixir may contain the active compound, water, alcohol or the like as the carrier, glycerol as solubilizer, sucrose as sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange.

Some of the active substances described: above form commonly known, pharmaceutically acceptable salts such as alkali metal and other common basic salts or acid addition salts, etc. References to the base substances are therefore intended to include those common salts known to be substantially equivalent to the parent compound.

The formulations as described above will be administered for a prolonged period, that is, for as long as the potential for a second heart attack remains or the symptoms continue. Sustained release forms of such formulations which may provide such amounts biweekly, weekly, monthly and the like may also be employed. A dosing period of at least one to two weeks are required to achieve minimal benefit.

The following Examples represent preferred embodiments of the invention.

Example 1

A pravastatin formulation in the form of tablets having the following composition was prepared as described below.

Ingredient	Parts by Weight
Pravastatin	7
Lactose	67
Microcrystalline cellulose	20
Croscarmellose sodium	2
Magnesium stearate	1
Magnesium oxide	3

Pravastatin, magnesium oxide and a fraction (30%) of the lactose were mixed together for 2 to 10 minutes employing a suitable mixer. The resulting mixture was passed through a #12 to #40 mesh size screen. Microcrystalline cellulose, croscarmellose sodium and the remaining lactose were added and the mixture was mixed for 2 to 10 minutes. Thereafter, magnesium stearate was added and mixing was continued for 1 to 3 minutes.

The resulting homogeneous mixture was then compressed into tablets each containing 5 mg, 10 m, 20 mg or 40 mg pravastatin which may be used in preventing or reducing risk of a second heart attack.

Example 2

Pravastatin tablets are prepared employing conventional pharmaceutical techniques containing 20 mg pravastatin and inert ingredients employed in lovastatin tablets, namely cellulose, color, lactose, magnesium stearate and starch and butylated hydroxyanisole as a preservative as described in the 1990 PDR.

The pravastatin tablets may be employed inactive ingredients to prevent or reduce risk of a second heart attack in accordance with the present invention.

Example 3

Tablets of the following compositions are prepared as described below.

Ingredient	Weight (mg)
SQ 33,600	100 mg
Avicel	112.5 mg
Lactose	113 mg
Cornstarch	17.5 mg
Stearic Acid	7 mg
	350 mg

The tablets are prepared from sufficient bulk quantities by slugging the SQ 33,600, Avicel, and a portion of the stearic acid. The slugs are ground and passed through a #2 screen and then mixed with the lactose, cornstarch, and the remainder of stearic acid. The mixture is compressed into 350 mg capsule shaped tablets in a tablet press. The tablets are scored for dividing in half.

The so-formed tablets may be administered in accordance with the teachings of the present invention to prevent or reduce risk of a second heart attack.

Examples 4

Lovastatin tablets are prepared employing conventional pharmaceutical techniques containing 20 mg lovastatin, cellulose, color, lactose, magnesium stearate and starch and butylated hydroxyanisole as a preservative as described in the 1990 PDR.

The lovastatin tablets may be employed to prevent or reduce risk of second heart attack in accordance with the present invention.

Example 5

A pravastatin formulation in the form of tablets is prepared as described in Example 1.

A captopril formulation suitable for oral administration together with pravastatin is prepared as described below.

1000 tablets each containing 25 mg of 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline were produced from the following ingredients.

1-[(2S)-3-Mercapto-2-methylpropionyl]-L-proline (captopril)	25 g
Corn starch	50 g
Gelatin	7.5 g
Avicel (microcrystalline cellulose)	25 g
Magnesium stearate	2.5 g

The captopril and corn starch are admixed with an aqueous solution of the gelatin. The mixture is dried and ground to a fine powder. The Avicel and then the magnesium stearate are admixed with the granulation. This is then compressed in a tablet to form 1000 tablets each containing 25 mg of active ingredient.

The pravastatin tablets and captopril tablets may be administered as a combination in accordance with the teachings of the present invention to prevent or reduce the risk of a second heart attack. In addition, the pravastatin and captopril tablets may be ground up into powders and used together in a single capsule.

Examples 6

Pravastatin tablets are prepared as described in Example 2.

The pravastatin tablets may be employed in combination with enalapril tablets containing 20 mg enalapril and inactive ingredients as described in the 1990 PDR, in separate or combined dosage forms to prevent or reduce the risk of a second heart attack in accordance with the present invention.

Example 7

Tablets containing SQ 33,600 prepared as described in Example 3 may be administered together with 25 mg captopril tablets to prevent or reduce risk of a second heart attack.

Examples 8

Lovastatin tablets are prepared employing conventional pharmaceutical techniques containing 20 mg lovastatin, cellulose, color, lactose, magnesium stearate and starch and butylated hydroxyanisole as a preservative as described in the 1990 PDR.

The lovastatin tablets may be employed alone or in combination with the captopril tablets (described in Example 5) or ceranapril tablets in separate or combined dosage forms to prevent or reduce risk of a second heart attack in accordance with the present invention.

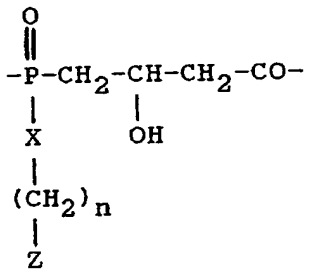
Claims

1. Use of an inhibitor of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase for manufacturing a medicament for preventing or reducing the risk of a second heart attack in a mammalian specie in need of such treatment.

2. The use as defined in claim 1 wherein said inhibitor of the enzyme HMG CoA reductase is mevastatin, lovastatin, pravastatin or velostatin.

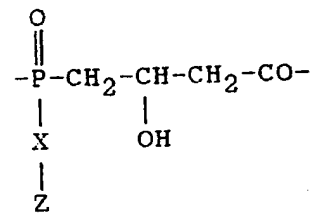
3. The use as defined in claim 1 wherein said inhibitor of the enzyme HMG CoA reductase is a pyrazole analog of a mevalonolactone, an indene analog of mevalonolactone, a 3-carboxy-2-hydroxy-propane-phosphinic acid derivative, a 6-[2-(substituted-pyrrol-1-yl)-alkyl]pyran-2-one, an imidazole analog of mevalonolactone, or a heterocyclic analog of mevalonolactone, a naphthyl analog of mevalonolactone, an octahydro-naphthalene, fluindostatin, a keto analog of lovastatin or a 2,3-di-substituted pyrrole, furan or thiophene.

4. The use as defined in claim 1 wherein the HMG CoA reductase inhibitor has the formula



wherein X is -O- or -NH-, n is 1 or 2 and Z is a hydrophobic anchor.

5. The use as defined in claim 1 wherein the HMG CoA reductase inhibitor has the formula



wherein X is $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-CH_2CH_2CH_2-$, $-C\equiv C-$ or $-CH_2O-$, where O is linked to Z, and Z is a hydrophobic anchor.

6. The use as defined in claim 1 wherein the HMG CoA reductase inhibitor is (S) -4[[[1-(4-fluorophenyl)-3-(1-methylethyl)-1H-indol-2-yl] -ethynyl]hydroxyphosphinyl]-3-hydroxybutanoic acid, or its disodium salt (SQ 33,600) or its dilithium salt.

7. The use as defined in claim 1 wherein the HMG CoA reductase inhibitor is pravastatin or SQ 33,600.

8. The use as defined in claim 1 wherein said medicament is manufactured in dosage forms containing 0.5 to 2000 mg HMG CoA reductase inhibitor for administration in single or divided doses/one to four times daily.

9. The use as defined in claim 1 further including an angiotensin converting enzyme inhibitor.

10. The use as defined in claim 9 wherein the angiotensin converting enzyme inhibitor is a substituted proline derivative.

11. The use as defined in Claim 9 wherein said angiotensin converting enzyme inhibitor includes a mercapto moiety and is a substituted proline derivative.

12. The use as defined in Claim 9 wherein said angiotensin converting enzyme inhibitor is a substituted proline derivative.

13. The use as defined in Claim 9 wherein said angiotensin converting enzyme inhibitor is captopril, zofenopril, enalapril, cernapril, fosinopril, lisinopril or fentiapril.

14. The use as defined in Claim 9 wherein the angiotensin converting enzyme inhibitor is a phosphonate substituted amino or imino acid or salt thereof, a proline derivative, a substituted proline derivative, a mercaptoacyl derivative of a substituted proline, a carboxyalkyl dipeptide derivative, a phosphinylalkanoyl proline derivative or a phosphonamidate derivative.

15. The use as defined in Claim 14 wherein said angiotensin converting enzyme inhibitor is a carboxyalkyl dipeptide derivative.

16. The use as defined in Claim 9 wherein said angiotensin converting enzyme inhibitor is a phosphinylalkanoyl proline derivative, a phosphoramidate derivative, or a phosphonate substituted amino or imino acid or salt thereof.

17. The use as defined in Claim 9 wherein the HMG CoA reductase inhibitor is present in a weight ratio to said ACE inhibitor within the range of 0.001:1 to 1000:1.

18. The use as defined in claim 9 wherein the HMG CoA reductase inhibitor is pravastatin.

19. The use as defined in claim 9 wherein said medicament is manufactured in dosage forms containing 0.1 to 500 mg angiotensin converting enzyme for administration in single or divided doses/one to four times daily.

20. The use as defined in claim 9 wherein the HMG CoA reductase inhibitor is pravastatin and the ACE inhibitor is captopril, fosinopril or ceranapril.

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(54) Method for preventing a second heart attack employing and HMG CoA reductase inhibitor.

(57) A method is provided for preventing or reducing the risk of a second heart attack by administering an HMG CoA reductase inhibitor such as pravastatin, alone or in combination with an ACE inhibitor.

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PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number: EP 91 10 9293

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,A	DE-A-3 817 375 (SQUIBB) * Claims * & GB-A-2 205 837 ---	4,5	A 61 K 31/365 A 61 K 31/22 A 61 K 31/40 A 61 K 31/66 A 61 K 31/00
D,A	DE-A-3 817 298 (SQUIBB) * Claims * & GB-A-2 205 838 ---	4,5	
E	EP-A-0 459 453 (SQUIBB) * Whole document * ---	1-20	
A	EP-A-0 373 507 (SQUIBB) * Abstract; page 2, lines 21-54 * ---	1-20	
X	PATENT ABSTRACTS OF JAPAN, vol. 7, no. 209 (C-186)[1354], 14th September 1983; & JP-A-58 109 416 (SANKYO K.K.) 29-06-1983 * Whole document * --- -/-	1,2,7,8	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A 61 K

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims

Claims searched completely : 1-3,6-20

Claims searched incompletely : 4,5

Claims not searched :

Reason for the limitation of the search:

The formulas given in claims 4 and 5 are incomplete.

Place of search	Date of completion of the search	Examiner
THE HAGUE	07-07-1992	GOETZ G.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
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